Review
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A Narrative Review on Clinical Trials Showing Contraindicated Drugs With Grapefruit Juice

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Abstract: Medication and food are frequently consumed together. However, some foods have interactions with medicines by changing key regulators of systemic medication availability. Their consumption is linked to interactions with a wide range of medications. One of the most significant beverages that can be harmful when combined with certain medicines is grapefruit juice. Furanocoumarins' mechanism-based suppression of intestinal cytochrome P450 3A4, which increases the bioavailability of drugs that are substrates, is the main mechanism by which interactions are mediated. There have also been reports of interactions between grapefruit products and uptake transporters such as P-glycoprotein (P-gp) and organic anion-transporting polypeptides (OATPs). It has been suggested that polyphenolic substances like flavonoids are what cause the interactions between P-gp and OATP. The amounts of furanocoumarins and flavonoids in the grapefruit product, the amount of juice consumed, the medium PH, and the inherent diversity of enzymes and transporter components in humans can all have an impact on the processes and magnitudes of interactions. In this review, we are going to shed light on clinical trials showing grapefruit juice-drug interactions and what should the health provider do for better clinical care.

Introduction

The citrus fruit genus, which also contains fruits like oranges, lemons, and limes, also includes the grapefruit, which has its origins on the Caribbean Island of Barbados. In 1837, botanist James Macfadyen gave grapefruit its initial scientific name, Citrus paradisi Macf (1). The development of grapefruit has a well-documented history, and molecular evidence largely supports the theory that it resulted from a natural cross between pummelo (Citrus maxima) and sweet orange (Citrus sinensis) (2-3). This fruit was very seedy with white flesh. Due to mutations, new species with different colors (pink, red) or seedless variations emerged (4). A well-balanced diet should include grapefruit. The fruit has been demonstrated to alter how several drugs are metabolized, raising the possibility of toxicity and negative side effects. The American Heart Association's "Healthy Heart Campaign" has endorsed grapefruit as a fruit to eat since it is low in calories and high in vitamin C, potassium, and dietary fiber (5). Most reported interactions between grapefruit juice and other grapefruit products and medications are caused by the suppression of intestinal CYP enzymes, specifically CYP3A4. The enzyme is completely rendered inactive as a result, and de novo restoration of the isoenzyme is required to prevent a protracted inhibitory effect on the intestinal clearance of the therapeutic drug. Inhibition of cellular transporter proteins, such as the efflux transporter P-glycoprotein (P-gp) and organic anion-transporting polypeptides (OATPs) mediating influx transport, are two additional mechanisms of grapefruit-drug interactions that have been described (6). The grapefruit seed extract is not the same as grapefruit juice, and it is unknown whether grapefruit seed extracts may also affect how drugs are metabolized. Inhibition of CYP3A4, CYP1A2, CYP2A6, P-gp, ATP-binding cassette drug transporters, and uptake transporters such as OATPs are some of the methods by which grapefruit may interact with pharmaceuticals (6-7). It appears that intestinal enzymes and the hepatic system are the primary pathways by which CYP is inhibited (7-8). According to studies, the half-life of CYP enzyme inhibition is roughly 12 hours, with a mean

of 62% inhibition remaining 5 days after grapefruit consumption (9). According to ambiguous findings in pharmacokinetic studies utilizing the substrates caffeine and theophylline, grapefruit juice's inhibitory action on the CYP1A2 isozyme appears to be modest and unsure. The large range of inhibitory flavonoids that exists among grapefruit juice formulations increases the uncertainty (8). Bergamot concentrations in grapefruit juice that were particularly chosen to have an impact on CYP3A4 with the substrate sunitinib were measured to be at least 23.5 and 2.7 mcmol/L, respectively (7).

Methodology for Review

The author searched a lot of databases, including PubMed, Google Scholar, Wiley Online, Scopus, and Science Direct, for clinical trials showing the potential for toxicity due to the coadministration of contraindicated drugs with grapefruit juice. The reference lists of papers were also hand-searched repeatedly to include additional clinical studies. Investigations and interpretations were made depending on the results of the clinical cases mentioned. These clinical trials prove the significant role of clinical pharmacists in all healthcare centers, including hospitals, clinics, and pharmacies.

Drugs When Co-administered With Grapefruit Juice, Its Serum Concentration Decreased

Aliskiren

Grapefruit juice may lower the level of aliskiren in the serum. Consider monitoring for lowered aliskiren efficacy if grapefruit juice is also taken. The ingestion of OATP2B1 by grapefruit juice, a transporter that may be involved in aliskiren gastrointestinal uptake, is the most likely mechanism of this interaction (10-11).

Celiprolol

Celiprolol, a drug that blocks beta-adrenergic receptors, was recently reported to be significantly reduced in plasma concentrations by grapefruit juice. During celiprolol medication, patients should refrain from consuming grapefruit and orange juice. Citrus juice-mediated suppression of the transporter SLCO2B1 (OATP2B1), which is in charge of absorbing celiprolol from the intestine, is most likely the main mechanism behind this interaction (12-15).

Clopidogrel

The active metabolite(s) of clopidogrel's serum concentrations may be reduced by grapefruit juice. When taking clopidogrel, patients must limit their intake of grapefruit and grapefruit juice. Three 200 mL glasses of grapefruit juice per day may significantly lessen the antiplatelet effects of clopidogrel. The primary mechanism of this interaction is thought to be grapefruit juice constituents inhibiting the metabolism of clopidogrel to its active metabolite, particularly via CYPs 3A4 and 2C19. In two phases, clopidogrel goes through oxidative metabolism to become its active metabolite. According to enzyme kinetics in vitro, CYP2C19 (45 percent estimated contribution), 1A2 (36 percent), and 2B6 (19 percent) catalyze the first step, while CYP3A4 (40 percent), 2B6 (36 percent), 2C19 (21%), and 2C9 (seven percent) catalyze the second.3 Although some findings suggest a potential dependence on other enzymes, such as CYP3A4 and CYP2C9, activation of clopidogrel appears to be mainly dependent on CYP2C19 activity based on in vivo evidence (16-17).

Etoposide

Grapefruit juice may lower the level of etoposide in the serum. Etoposide that is taken orally is the only medication that interacts with it. When taking oral etoposide along with grapefruit juice, keep an eye out for diminished etoposide effectiveness. Although the exact mechanism of this interaction is unknown, grapefruit juice-mediated suppression of the OATPs (OATP1A2 or OATP2B1) that may be involved in etoposide intestinal absorption, may conceivably contribute (18).

Fexofenadine

Grapefruit Juice decreases the serum concentration of Fexofenadine. Monitoring patients for decreased effects of fexofenadine with concomitant administration of grapefruit juice is recommended. Separating fexofenadine administration and grapefruit juice consumption by at least 4 hours may avoid this interaction. The mechanism of this interaction is likely grapefruit juice inhibition of OATP2B1, a transporter responsible for fexofenadine absorption (15, 19-26).

Drugs When Co-administered With Grapefruit Juice, Its Serum Concentration Increased

Amiodarone

The serum level of amiodarone rises after consumption of grapefruit juice. Amiodarone's primary metabolite, N-DEA, is completely inhibited from being produced by grapefruit juice, which has a severe impact on amiodarone metabolism. When taking amiodarone, patients should refrain from drinking grapefruit juice. The grapefruit-mediated suppression of CYP3A4, an enzyme responsible for amiodarone metabolism, is most likely the mechanism behind this interaction (27).

Atorvastatin

The amount of atorvastatin in the blood may rise after drinking grapefruit juice. It's not advised to combine atorvastatin with a lot of grapefruit juice (more than 1.2 liters per day). Patients who eat lesser amounts of grapefruit juice, or whose grapefruit juice intake has

recently changed or is changeable, should be watched for signs and symptoms of atorvastatin side effects (such as myopathy, rhabdomyolysis, etc.). The capacity of various components of grapefruit juice to inhibit CYP3A4 is primarily responsible for this interaction's mechanism. It is also conceivable for GFJ to modify the way atorvastatin is transported (for instance, using P-gp or other efflux transporters) (28, 29).

Artemether

The serum concentrations of the active metabolite(s) of artemether may rise when grapefruit juice is consumed. Dihydroartemisinin (DHA), the active metabolite of artemether, may be present in higher amounts. The blood concentration of Artemether may rise after drinking grapefruit juice. If you take artemether with grapefruit or grapefruit juice, keep an eye out for any increased toxicity, such as QTc interval prolongation. Avoiding grapefruit juice during treatment may be a better management strategy because artemether therapy is only given for three days. The grapefruit juice-mediated suppression of CYP3A4, an enzyme involved in the metabolism of artemether, is the mechanism underlying this possible interaction (30).

Buspirone

The serum concentration of BusPIRone may rise after consuming grapefruit juice. Large amounts of grapefruit juice should not be consumed by patients when taking buspirone. If patients drink grapefruit juice while taking buspirone, keep an eye out for any increased side effects. The capacity of some components of grapefruit juice to inhibit CYP3A4 isoenzymes (mainly in the small intestine) and hence prevent the metabolism of buspirone is most likely the mechanism underlying this interaction (31, 32).

Oral Budesonide

Grapefruit juice (GFJ) reduces the first-pass metabolism of CYP3A substrates by inhibiting CYP3A activity in the gut wall. Regular use of grapefruit juice increased both delayed-release budesonide and plain budesonide's bioavailability twofold. If inhaled budesonide is administered to a patient who is taking a mild CYP3A4 inhibitor, it is preferable to monitor patients for indications and symptoms of corticosteroid excess. The most plausible mechanism of this interaction is suppression of budesonide's CYP3A substrate CYP3A4 metabolism by CYP3A4 inhibitors (33).

Cilostazol

Cilostazol's serum levels may rise in response to CYP3A4 Inhibitors (Moderate). In patients taking mild CYP3A4 inhibitors, the dosage of cilostazol must be reduced to 50 mg twice daily. The most plausible mechanism of action for this interaction is the suppression of cilostazol's CYP3A4-mediated metabolism by mild CYP3A4 inhibitors (34).

Cisapride

The serum levels of cisapride may rise in response to moderate CYP3A4 inhibitors. Alternatives to this combination should be taken into account. Although some experts advise monitoring and dose titration, the coadministration of CYP3A4 inhibitors with cisapride is not advised. Inhibition of CYP3A4, an enzyme involved in the metabolism of cisapride, is the mechanism behind this interaction (35-38).

Colchicine

Colchicine serum levels may rise after drinking grapefruit juice. It is advised to stay away from grapefruit juice while using colchicine. The mechanism of this interaction is probably grapefruit juice-mediated intestinal CYP3A4 inhibition, an enzyme involved in the metabolism of colchicine (39, 40).

Cyclosporine

The systemic Cyclosporine metabolism may be slowed down by grapefruit juice. If grapefruit juice is drunk while receiving therapy, monitoring for elevated serum concentrations and the effects of orally delivered cyclosporine is required. Grapefruit or grapefruit juice shouldn't be consumed while taking cyclosporine. The most likely cause of this interaction is grapefruit juice's suppression of intestinal CYP3A4, which increases the amount of cyclosporine that is available for absorption (41, 42).

Carbamazepine

The level of Carbamazepine in the serum may rise after drinking grapefruit juice. Patients who drink grapefruit juice should be watched for elevated carbamazepine levels and toxicity (such as ataxia, sleepiness, vertigo, and diplopia). It may be necessary to reduce the dosage of carbamazepine when using CYP3A4 inhibitors concurrently. The primary enzyme in charge of carbamazepine metabolism, CYP3A4, is known to be inhibited by a few components in grapefruit juice. Taking grapefruit at the same time as carbamazepine will likely lessen the drug's ability to be metabolized by CYP3A4 in the body. (53).

Clomipramine

The amount of Clomipramine in the serum may rise after drinking grapefruit juice. If you regularly administer grapefruit juice alongside clomipramine, keep an eye out for any enhanced systemic effects. If you stop regularly administering grapefruit juice, watch out for any decreased effects. The most likely mechanism of this interaction is grapefruit juice components inhibiting CYP3A4-mediated clomipramine metabolism (54).

Codeine

The active metabolite(s) of codeine may be present in higher serum quantities after taking CYP3A4 inhibitors. Watch for improved therapeutic effects of codeine if a moderate CYP3A4 inhibitor must be administered concurrently. Consider reducing the dosage of codeine until steady medication effects are reached while keeping an eye out for respiratory depression and other side effects. If a moderate CYP3A4 inhibitor is stopped, keep an eye out for diminished codeine therapeutic benefits. As soon as the drug's effects become stable, consider increasing the dose of codeine while keeping an eye out for opioid withdrawal symptoms. The most plausible mechanism of this interaction is the suppression of the metabolism of codeine by CYP3A4 to its inactive metabolite norcodeine, which leaves more codeine available for CYP2D6 conversion into morphine (55).

Diazepam

The blood levels of DiazePAM may rise when using CYP3A4 Inhibitors (Moderate). If you combine diazepam with mild CYP3A4 inhibitors, keep an eye out for increased side effects and toxicities (such as somnolence and drowsiness). The suppression of CYP3A4, an enzyme responsible for the metabolism of diazepam, is most likely the mechanism of this interaction (44).

Dapoxetine

Dapoxetine's serum concentration is raised by grapefruit juice. It is advised to stay away from grapefruit juice for 24 hours before or during dapoxetine administration. The suppression of CYP3A4, an enzyme involved in the metabolism of dapoxetine, is most likely the mechanism of this interaction (56).

Erythromycin

The serum concentration of systemic erythromycin may rise in response to moderate CYP3A4 inhibitors. When used with mild CYP3A4 inhibitors, watch out for enhanced erythromycin effects and toxicities, including as QTc interval lengthening. The suppression of the erythromycin metabolism-related enzyme CYP3A4 is most likely the mechanism of this interaction (57-60).

Felodipine

The serum levels of felodipine may increase after drinking grapefruit juice. Patients who drink grapefruit juice should have their hemodynamic response to felodipine regularly monitored (e.g., blood pressure, and heart rate). It could be necessary to modify the dosage of felodipine or the way that grapefruit juice is consumed. The bioavailability (and AUC) of felodipine is raised as a result of this interaction, which appears to be caused by the suppression of CYP3A-mediated felodipine metabolism in the intestine. While medications like amlodipine and nifedipine are among those least likely to interact severely with GFJ, felodipine is one of the calcium channel blockers most likely to do so (44, 61-78).

Fluvoxamine

Fluvoxamine serum levels may rise when consumed with grapefruit juice. Consider keeping an eye out for patients who regularly consume significant amounts of grapefruit products for fluvoxamine to see if there are any increased systemic effects. Unknown is the mechanism behind this connection (54, 79).

Halofantrine

Halofantrine's serum levels may rise in response to moderate CYP3A4 inhibitors. The use of halofantrine in conjunction with any mild CYP3A4 inhibitor(s) should be done with extreme caution, and perhaps increased heart state monitoring (e.g., ECG). The apparent mechanism of this interaction is the suppression of the halofantrine metabolism-related enzyme CYP3A4 (80).

Ibrutinib

Ibrutinib serum levels may rise when consumed with grapefruit juice. While using ibrutinib, patients should refrain from consuming grapefruit or grapefruit juice. Grapefruit juice-mediated suppression of the intestinal CYP3A4 enzyme, which is in charge of ibrutinib metabolism, is the mechanism behind this interaction. (81).

Ivabradine

Grapefruit juice may raise the drug's serum levels. During ivabradine treatment, patients must refrain from consuming grapefruit or grapefruit juice. It is anticipated that grapefruit consumption will enhance ivabradine exposure and the risk of toxicity, especially when consumed often and/or in large amounts. The suppression of CYP3A4, an enzyme responsible for the metabolism of ivabradine, is most likely the mechanism of this interaction (82).

Oral Ketamine

The level of ketamine in the serum may rise after drinking grapefruit juice. If oral ketamine is used with grapefruit juice, keep an eye out for any increased toxicities or effects of ketamine (such as drowsiness or dissociation). The gastrointestinal CYP3A4 enzyme, which is partially in charge of ketamine metabolism, is most likely inhibited by grapefruit juice, which accounts for the mechanism of this interaction. Only when ketamine is taken orally can this interaction be anticipated to happen. When ketamine is administered by methods that avoid the gastrointestinal tract (such as intravenous, and nasal), no interaction is predicted (83).

Lovastatin

The active metabolite(s) of lovastatin may have higher

serum concentrations when grapefruit juice is consumed. The blood levels of lovastatin may rise when consumed with grapefruit juice. Patients taking lovastatin must refrain from consuming grapefruit juice. The capacity of some GFJ components to inhibit CYP3A4 appears to be the primary factor in this interaction's mechanism. It is also feasible for certain HMG-CoA reductase inhibitor trafficking to be altered by the GFJ (e.g., via p-glycoprotein and/or other efflux or uptake transporters) (34, 84).

Methadone

The serum concentration of methadone may rise in response to moderately potent CYP3A4 inhibitors. Consider lowering the dose of methadone if coadministration with mild CYP3A4 inhibitors is required until steady effects are attained. Patients should be constantly watched for sedation and respiratory depression. If a mild CYP3A4 inhibitor is stopped, keep an eye out for symptoms of opioid withdrawal in patients and think about increasing the dose of methadone until stable medication effects are reached. increase in methadone plasma levels may intensify the drug's negative effects, such as deadly respiratory depression. The suppression of CYP3A4, an enzyme involved in the partial metabolism of methadone, is most likely the mechanism underlying this interaction (89).

Midazolam

Midazolam's serum levels may rise in response to CYP3A4 Inhibitors (Moderate). Avoid taking moderate CYP3A4 inhibitors with nasal midazolam at the same time. If these medications are combined, patients should be closely watched for any increased and extended oral midazolam effects and toxicities (such as sedation, and respiratory depression). When compared to other methods of administering midazolam, oral midazolam appears to have a stronger impact on the size and clinical outcomes of this interaction. It is best to avoid using nasal midazolam when using mild CYP3A4 inhibitors. Because CYP3A4 inhibition is known to produce drowsiness, oral midazolam should be used with caution for patients receiving these medications. Take into account using lower oral midazolam doses, and thoroughly observe patients. Use of IV and IM midazolam in combination with CYP3A4 inhibitors should be done cautiously, and extended monitoring of midazolam effects is advised. The suppression of CYP3A4, an enzyme involved in the metabolism of midazolam, is the mechanism behind this interaction. This interaction is most likely more significant and concerning with oral midazolam than with other methods of midazolam administration because oral midazolam inhibits both gastrointestinal and hepatic CYP3A4 simultaneously (7, 15, 44, 54, 56, 85, 90-100).

Manidipine

Manidipine's serum levels may rise when taken with CYP3A4 Inhibitors (Moderate). If manidipine is taken along with a mild CYP3A4 inhibitor, keep an eye out for any increased side effects and toxicities. Although there are no guidelines for usage with mild CYP3A4 inhibitors, it is likely necessary to monitor patients for manidipine toxicity when these medications are taken together. The suppression of CYP3A4, an enzyme involved in the metabolism of manidipine, is most likely the mechanism of this interaction (101).

Methylprednisolone

Methylprednisolone serum levels may be raised by CYP3A4 Inhibitors. If you combine methylprednisolone with a potent CYP3A4 inhibitor, keep an eye out for any enhanced side effects. Inhibition of CYP3A4 leading to a reduction in methylprednisolone metabolism is the most probable mechanism for this interaction (102).

Nitrendipine

The serum levels of Nitrendipine may rise after consuming grapefruit juice. In patients who drink grapefruit juice, watch out for an exaggerated hemodynamic reaction (i.e., lowered blood pressure and increased heart rate) to oral nitrendipine. The first-pass metabolism of nitrendipine, which is mediated by CYP3A, appears to be inhibited in this interaction, increasing the bioavailability (and AUC). In terms of how strongly it might interact with GFJ among the calcium channel blockers examined, nitrendipine rates are about in the center (44, 103-104).

Nilotinib

The serum concentration of nilotinib may rise after drinking grapefruit juice. If grapefruit juice is consumed while with nilotinib, monitoring is required for increased toxicities and side effects. It is crucial to advise patients to stay away from grapefruit juice to prevent this interaction. The mechanism of this interaction is most likely caused by intestinal CYP3A4, which is in charge of nilotinib first-pass metabolism, being inhibited by grapefruit juice (105).

Nifedipine

The blood levels of Nifedipine may rise after consuming grapefruit juice. It is advised not to take nifedipine and grapefruit juice at the same time. The first-pass CYP3A-mediated metabolism of nifedipine in the intestine appears to be inhibited by GFJ in this interaction, increasing the drug's bioavailability and AUC. Drugs with higher lipophilicity, lesser bioavailability, and less protein binding have been found to interact more strongly with GFJ, according to studies with nifedipine and other calcium channel blockers (44, 106-107).

Nimodipine

The serum level of Nimodipine may rise after drinking

grapefruit juice. Patients must refrain from taking nimodipine and grapefruit juice at the same time. It is most likely that intestinal CYP3A4, an enzyme responsible for nimodipine metabolism, is inhibited by grapefruit juice as the mechanism of this interaction (108).

Nisoldipine

The serum levels of Nisoldipine may rise after drinking grapefruit juice. Patients must refrain from consuming grapefruit juice and nisoldipine together. Nisoldipine's CYP3A-mediated intestinal metabolism appears to be inhibited by this interaction, increasing the drug's bioavailability (44, 104, 109-110).

Oxycodone

The serum concentration of Oxycodone may rise in response to CYP3A4 inhibitors. The active metabolite Oxymorphone's serum concentrations could also rise. When oxycodone is coadministered with a CYP3A4 inhibitor, patients should be checked more regularly for enhanced opioid effects (such as drowsiness and respiratory depression), and the dose of oxycodone may need to be reduced until stable drug effects are reached. If a CYP3A4 inhibitor is stopped, keep an eye out for diminished opioid effects or withdrawal symptoms and think about increasing the dosage of oxycodone until stable medication effects are reached. If a CYP2D6 inhibitor is also used along with a CYP3A4 inhibitor and oxycodone, the strength of this interaction may be increased. Inhibition of CYP3A4, an enzyme that is partially in charge of the bulk of oxycodone metabolism, is the mechanism underlying this interaction (55).

Praziquantel

The serum levels of Praziquantel may rise after drinking grapefruit juice. When using praziquantel and grapefruit juice simultaneously, patients should be watched for any increased side effects or toxicity. The suppression of CYP3A4, an enzyme involved in the metabolism of praziquantel, is most likely the mechanism of this interaction (111).

Quinidine

Quinidine serum levels may rise when consumed with grapefruit juice. Patients must refrain from taking quinidine and grapefruit juice at the same time. The observed rise in quinidine concentrations is most likely caused by grapefruit juice's suppression of intestinal CYP3A4. It is unknown how grapefruit juice could slow down the absorption of quinidine (112-113).

Ritonavir

Ritonavir's serum levels may rise in response to CYP3A4 inhibitors. When taking mild CYP3A4 inhibitors with ritonavir, keep an eye out for any worsened side effects, such as elevated transaminases, nausea, vomiting, and diarrhea. The inhibition of CYP3A4, an enzyme involved in the metabolism of ritonavir, is the mechanism behind this interaction (114-115).

Simvastatin

The blood levels of Simvastatin may rise after drinking grapefruit juice. Simvastatin-treated patients should refrain from consuming grapefruit juice. For patients who consume large amounts of grapefruit juice or for patients whose grapefruit juice consumption is highly variable, fluvastatin, pitavastatin, pravastatin, and rosuvastatin all appear to be at particularly low risk for any clinically significant interaction with even greater amounts of grapefruit juice. These medications may be suitable alternatives. The capacity of some GFJ components to inhibit CYP3A4 appears to be the primary factor in this interaction's mechanism. It is also feasible for certain HMG-CoA reductase inhibitor trafficking to be altered by the GFJ (e.g., via p-glycoprotein and/or other efflux or uptake transporters) (116-119).

Saquinavir

Saquinavir's serum levels may rise in response to moderate CYP3A4 inhibitors. If you co-administer mild CYP3A4 inhibitors with saquinavir, keep an eye out for any enhanced saquinavir side effects (such as nausea, diarrhea, or elevated hepatic transaminases). The CYP3A4 enzyme, which is in charge of saquinavir metabolism, is inhibited as the mechanism of this interaction (120).

Sertraline

The blood levels of sertraline may rise after drinking grapefruit juice. Patients who consume grapefruit products should be watched for increased systemic effects of sertraline, especially if consumption is frequent and substantial. It is unclear how this connection works exactly. Although CYP3A4 is not the main pathway for sertraline elimination, grapefruit juice components may impede CYP3A4-mediated sertraline metabolism (121).

Sildenafil

The serum concentration of Sildenafil may rise after drinking grapefruit juice. If sildenafil is taken with grapefruit juice, keep an eye out for any potentially harmful effects. This interaction appears to be mediated by intestinal CYP3A4, an enzyme involved in the metabolism of sildenafil, which is inhibited by grapefruit juice (122).

Tacrolimus

Tacrolimus may be less efficiently metabolized when consumed with grapefruit juice. Patients must refrain from taking tacrolimus with grapefruit or grapefruit juice at the same time. Grapefruit inhibition of intestinal CYP3A, which results in lower metabolism

and increased bioavailability of oral tacrolimus, is the most likely mechanism for this reported interaction (123).

Tolvaptan

Tolvaptan content in the serum may rise after drinking grapefruit juice. When taking tolvaptan, patients should refrain from drinking grapefruit juice. Inhibition of CYP3A4, which is in charge of the metabolism of tolvaptan, is the most likely mechanism for this interaction (124).

Triazolam

Triazolam's serum levels may rise in response to moderately potent CYP3A4 inhibitors. Reduce the dose of triazolam if the patient is also taking a mild CYP3A4 inhibitor. The suppression of CYP3A4, an enzyme involved in the metabolism of triazolam, is most likely the mechanism of this interaction (31, 44, 54, 94, 96, 114, 125-129).

Terfenadine

Terfenadine's serum levels may rise when taken with CYP3A4 Inhibitors (Moderate). When terfenadine is used alongside mild CYP3A4 inhibitors, keep an eye out for elevated terfenadine concentrations as well as any negative side effects, such as QTc prolongation. Inhibition of CYP3A4, an enzyme responsible for terfenadine metabolism, is the mechanism behind this interaction (19, 20, 21, 22, 23, 24, 26, 44, 130-132).

Ticagrelor

The blood levels of ticagrelor may rise when consumed with grapefruit juice. Watch out for enhanced systemic effects of ticagrelor in patients who consume grapefruit products, especially when consumption is frequent and in large amounts. Examples include signs and symptoms of bleeding or easy bruising and changes in platelet function tests when watched. One or more components of grapefruit juice are thought to inhibit the CYP3A4-mediated metabolism of ticagrelor, which is the primary mechanism of action of this interaction (133).

Verapamil

The serum concentration of verapamil may rise when consumed with grapefruit juice. When used with grapefruit juice, verapamil toxicities (such as hypotension and bradycardia) may worsen. The grapefruit juice-induced suppression of CYP3A4, an enzyme involved in the metabolism of verapamil, is the mechanism behind this interaction (134-137).

Vinblastine

Vinblastine's serum levels may rise in response to moderate CYP3A4 inhibitors. When using CYP3A4 inhibitors in combination with vinblastine, keep an eye out for enhanced toxicities. The suppression of CYP3A4, an enzyme involved in the metabolism of vinblastine, is most likely the mechanism behind this interaction. P-gp inhibition could be a factor (26).

Drugs Have Two Opposite Effects When Co-administered With Grapefruit Juice

Itraconazole

Grapefruit juice may lower the level of itraconazole in the blood. The serum concentration of itraconazole may rise when grapefruit juice is consumed. If grapefruit juice is consumed at the same time as itraconazole, keep an eye out for any altered effects. Both increased and decreased itraconazole concentrations have been recorded. Encourage patients not to change their grapefruit or grapefruit juice intake habits without first speaking to their doctor. The precise itraconazole dosage form and perhaps the dose/strength of grapefruit juice appear to affect how grapefruit juice interacts with it. It's unclear what causes this ostensible interaction. The cause of a decreased itraconazole AUC (or even the lack of an impact) with grapefruit juice (which is acidic and an inhibitor of intestinal CYP3A) is unknown for itraconazole oral capsules, whose systemic availability is decreased at higher gastric pH values. Other probable explanations include altered stomach motility and/or altered intestinal drug transporters (grapefruit juice is known to block a variety of efflux and uptake transporters). The modest increase in itraconazole availability for itraconazole oral solution, which is less sensitive to gastric pH, appears to be caused by grapefruit juice-mediated suppression of CYP3A metabolism in the intestines, while a role for transporter inhibition is also possible (35, 128, 138-142).

Conclusion

Several regularly used drugs can be affected by grapefruit products' pharmacokinetics, but many of these interactions aren't regarded to be clinically important. The pharmacodynamics and clinical effects of grapefruit interactions can occasionally be ambiguous when grapefruit products are consumed frequently or infrequently, as well as because active component variations occur between different grapefruit products. Furthermore, individual differences in endogenous CYP3A4 and transporter proteins add to the complexity of the issue. Depending on the factors affecting the drug's metabolism and distribution, grapefruit products may increase or decrease exposure. However, as seen by a rise in side effects or a fall in efficacy, a change in a drug's pharmacokinetics may not always have a direct impact on its pharmacodynamics. GFJ decreases the serum concentration of the following drugs: Aliskiren,

Celiprolol, Clopidogrel, Etoposide, and Fexofenadine, so their effect is decreased. GFJ increases the serum concentration of the following drugs: Amiodarone, Atorvastatin, Artemether, Oral budesonide, BusPIRone, Carbamazepine, Codeine, Colchicine, Cyclosporine, Cilostazol, Cisapride, Clomipramine, Dapoxetine, Diazepam, Erythromycin, Felodipine, Fluvoxamine, Halofantrine, Ibrutinib, Ivabradine, Oral Ketamine, Lovastatin, Methadone, Manidipine, Midazolam, Methylprednisolone, Nilotinib, Nifedipine, Nimodipine, Nisoldipine, Nitrendipine, Oxycodone, Praziquantel, Quinidine, Ritonavir, Simvastatin, Saquinavir, Sertraline, Sildenafil, Tacrolimus, Tolvaptan, Terfenadine, Ticagrelor, Triazolam, Verapamil, Vinblastine, so adverse effects potentiate. GFJ has two opposite effects on itraconazole, and the mechanism is unknown. Not all contraindicated drugs should be avoided but may be used when necessary, with monitoring and considering lower doses. Some drugs' interactions with GFJ depend on the route of administration such as budesonide, midazolam, and ketamine.

List of Abbreviations

CYP: cytochrome P-450 enzymes; OATPs: Organic Anion Transporting Polypeptides; SLCO2B1: Solute carrier organic anion transporter family member 2B1; P-gp: permeability glycoprotein; ATP: Adenosine triphosphate; GFJ: Grapefruit Juice.

Declarations

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Contribution: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

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